February 7, 2003

Dr. Leslie Ball
Office for Human Research Protections
Department of Health and Human Services
The Tower Bldg., 1101 Wootton Pkwy., Suite 200
Rockville, MD 20852

Subject: UNC-Chapel Hill Request for HHS Review under 45 CFR 46.407
Re: P50 HL 60280 – Dr. R. Boucher (Grant PI) – Dr. T. Noah (Project PI)

Dear Dr. Ball:

Please accept this in response to Clifford Scharke's letter to one of us (DKN), dated October 24, 2002. It is our understanding that you have assumed responsibility for coordinating this review. We appreciate the substantive nature of questions raised, and have consulted further with IRB members and the investigator, in order to answer them completely. We are providing the additional information for each point raised by OHRP:

Missing items requested

You may already have some of these items from interim correspondence, but we are enclosing a copy of the award application and the minutes of the IRB meetings in which the deliberations regarding this study took place. [Appendix IA and IB]. We are assuming that you still have all materials previously submitted, so we are not re-enclosing all here.

Scientific value of the proposed study

The scientific value of this study has been reviewed by the IRB and with Dr. Terry Noah, the Principal Investigator. Background information supporting our analyses and conclusions is summarized in the following paragraphs:

Prognosis and Proposed Disease Model

This study addresses the underlying pathogenesis of cystic fibrosis (CF). This disease is fatal in 85 to 90 % of individuals by the 4th decade of life without a lung transplant. There are proposed mechanisms by which cystic fibrosis is thought to exert its effects on pulmonary physiology. In the model supported by medical scientists at the University of North Carolina, there is thought to be excess isotonic volume transport in the distal airways with subsequent development of thickened mucus resulting in mucus plugging. This mucus plugging predisposes the lungs to infection.

This lack of water also impairs mucociliary clearance by decreasing mechanical advantage. This decrease in mucociliary clearance leads to stasis of inhaled microbes. *Pseudomonas* has a special tendency to form biofilms. Bacterial biofilm formation may occur early in life (weeks to months after birth). Resulting inflammation is persistent and neutrophil-dominated, leading to progressive bronchiectasis and eventual death from respiratory failure.

The predicted effect of the above would be 1) accumulation of mucus (mucins plus other compounds) in distal airways, even prior to onset of infection/inflammation; and 2) a qualitative change in mucus density. Because chronic infection becomes established so early in life in CF patients, this initiating event (accumulation of mucus) can likely be detected only in the first weeks to months after birth. After that time, infection and inflammation (with secondary effects on mucus hypersecretion) are likely to obscure the original defect.

Existing Models in Cystic Fibrosis

Pathology studies in older CF patients show increased expression of MUC5AC (one of the major mucins in airway) compared to normals[1], though there has also been reported decreased MUC5AC expression in nasal epithelium from CF patients[2]. [Appendix II – References]. Cell culture and mouse models (CFTR knockouts) for CF airway disease do show some evidence of reduced mucociliary clearance[3]. However, these models have been disappointing for several reasons, as described by A.S. Verkman[4] in a recent editorial:

> "The testing of these hypotheses has presented a formidable challenge because of difficulties in establishing suitable model systems…cell culture models have been highly variable from laboratory to laboratory; they cannot recapitulate the complex in vivo airway anatomy, hormonal regulation, and cellular heterogeneity….lung disease in mouse models of cystic fibrosis is quite subtle. Also, there are a number of potentially important human versus mouse species differences in airway physiology; airway submucosal glands are essentially absent from mouse airways below the larynx, and the mouse airway epithelium appears to express an alternative C1 channel that may substitute for functionally defective CFTR. Measurements in intact normal versus cystic fibrosis human airways are probably the most appropriate for studying ASL properties, recognizing the caveat that human airway anatomy and function are altered in response to recurrent infection and inflammation."

Knowledge that may be obtained from proposed human study

Based on the above, the IRB agreed with Dr. Noah that human studies remain of unique value in CF research. Numerous infant bronchoalveolar lavage fluid (BALF) studies have been performed and published related to onset of infection and inflammation in CF, many from the PI's laboratory[5-7], some for research indications only (at other institutions), and none with adverse events reported. To date, no studies addressing mucus/mucin in early CF have been reported, nor do our local investigators (among the leaders in the country in

this area) know of any such studies in progress. This is because the methods for measurement of these factors have only recently become available – and only at a handful of research centers.

The proposed study thus seeks to measure certain mucus and mucin characteristics in young CF patients, while potentially providing the direct benefit of early identification of bacterial infections for early initiation of specific treatment with antibiotics. Parameters measurable with current technology include MUC5AC and MUC5B quantity (by ELISA) and histological assessment of mucus plugs to determine their biochemical, cellular and microbial contents.

The primary significance of the proposed study would be increased understanding of the pathogenesis of CF lung disease at its earliest stages. This could have an impact on treatment, perhaps even for the subjects who would be involved in the immediate study. Several strategies for improvement of mucus abnormalities in CF are actively being investigated at present in older patients, including use of hypertonic saline[8] , Nacystelyn[9], and mannitol[10]. These agents are designed to improve lysis and hydration of mucus. It is possible that promising agents would move quickly to clinical trials in infants and children with CF, if evidence favored an initial accumulation of mucus as the starting point for CF airway disease.

Subject population with proposed study

Subjects that would be included in this study are children from age 0-2 years. All these children will have the diagnosis of cystic fibrosis. However, the children will not have received any inhaled steroids or oral drugs to reduce inflammation prior to bronchoscopy. Children who have signs of active infection or respiratory symptoms will be excluded.

Considerations of IRB in review of the study

This study was reviewed by the convened IRB on 3 occasions: 12/17/01, 02/04/02, and 04/15/02. We are enclosing copies of minutes from all three dates [Appendix IB – Missing Items]. We call your attention to the memo dated 02/05/02, in which we discuss the rationale for IRB disapproval and our recommendation that this study be referred to OHRP for review by the panel of experts convened under 45 CFR 46.407.

In our memo dated 02/05/02, we note that bronchoscopy in an asymptomatic infant is not indicated. Children at this age are unable to expectorate or provide sputum samples. Regardless of the pathogenesis of this disease, these mechanisms ultimately lead to an increased incidence of colonization and ultimately infection within the lung.

When we reviewed this study on 02/04/02, with the information provided, we had concluded that bronchoscopy in asymptomatic infants was not indicated. Because we felt that bronchoscopy is a procedure which represents greater than minimal risk in this population, and because the prospect of direct benefit was uncertain, the IRB felt that

categories 46.404 and 46.405 were not applicable. Similarly, because the IRB felt that the risk of bronchoscopy in an asymptomatic infant was of sufficient magnitude to be beyond

that described as a minor increase over minimal risk, we found that we could not approve this study under category 46.406. These findings were reaffirmed in a third consideration by the IRB in April, 2002.

The IRB did conclude, however, that because of the scientific basis for this study and because there was a strong possibility of furthering the understanding of pulmonary disease in cystic fibrosis, the study had sufficient merit to be considered under Category 46.407.

If a subsequent study were to show that early intervention with antibiotics in asymptomatic infants with colonization by pseudomonas delayed or prevented the progression of the pulmonary pathology in infants with cystic fibrosis, this would represent a shift in the thinking about the management of this disease.

At the time we made our initial determination in December 2001, and again in February and April, 2002, we felt that the risk of the bronchoscopic procedure would constitute greater than minimal risk, which was not offset by potential benefit in the asymptomatic population. We did query Dr. Noah about the alternative of enrolling children who already had lung disease (i.e. were symptomatic). He noted that "the published rates for infection for clinically-indicated procedures compared to research procedures are quite similar. In essence, clinical symptoms are poor predictors of chronic bacterial airways infection in cystic fibrosis. Chronic infection, not acute infection, is the main determinant of progressive lung disease and death". (See Noah response memo from March 2002). Thus, limiting enrollment to symptomatic children would miss many who were already infected.

Dr. Noah's response to the IRB memo dated 02/05/02 also addressed the question of early treatment of *pseudomonas* or other pathogens. Recent information has been presented at a meeting of investigators of cystic fibrosis in Europe which looked at early intervention with antibiotics. The preliminary results have not shown a problem with resistance to infection developing early. This data from the Copenhagen Cystic Fibrosis Center also suggests that the outcomes are certainly not worse and may be dramatically improved. (T. Noah, personal communication).

Bronchoscopy clinical protocol

In response to OHRP's request, we are providing additional information about the standard clinical protocols used in the bronchoscopy laboratory at UNC. [Appendix III – Conscious Sedation Policy and Bronchoscopy Cleaning Protocol].

The frequency of adverse events with bronchoscopy remain the same with repeated bronchoscopies even if they are performed within a relatively short period of time. There is no cumulative effect. Data from the literature on pediatric flexible bronchoscopy is referenced in the table below, taken from an article by Barbato[11].

	< 5% of procedures	5-10% of procedures	>10% of procedures
During flex. Bronchoscopy			
Bleeding	33	2	-
Bronchospasm	34	2	2*
Laryngospasm	35	-	1*
Drug reactions	32	2	1*
After flex. Bronchoscopy			
Bronchospasm	34	2	-
Cough	16	19	2
Fever	30	5	3
Laryngospasm	33	1	-

Numbers are centers out of 51 surveyed. * Reported by centers performing <100 procedures per year.

A second article by Schellhase reported 30 procedures in children with recurrent wheeze. Of these 7 had transient hypoxemia, 2 had fever within 12 hr, 1 had transient bradycardia. None of these complications prevented completion of the procedure or prolonged the recovery.[12]

UNC experience with infants undergoing bronchoscopy

None of these aforementioned published series break the data down by age group into infants versus older children. Dr. Noah has provided his data for 2171 bronchoscopy procedures performed at UNC from November 1998 until the present. The incidence for any complication was less than 1%. The incidence was the same or lower for 432 infants undergoing bronchoscopy. [Appendix IV – Complication Data at UNC].

Inducements for participation

The IRB considered the amount of compensation to subjects in the course of three separate reviews. The IRB determined that the inducements offered in the study to both children and their parents are reasonable because of a 3-day stay in the hospital, as well as the travel and time loss for work. It was felt that the inducement offered directly for the children sends a signal to the parents that this money should be used for the child's benefit. We would, however, be willing to reconsider this issue should the expert panel have other opinions.

Modification of parental permission form

OHRP questioned the lack of compensation for research-related injury. While the IRB does not necessarily endorse this lack of coverage, the standard consent form language reflects current UNC policy. As OHRP is aware, the regulations [45 CFR 46.116(a)(6)] only require that subjects be provided an explanation as to whether any compensation is available, and not that such compensation must be provided. Regrettably, the IRB is not in a position to alter institutional and/or state policy, on an ad hoc basis. We have, however, secured a commitment from the PI and his Division to waive any professional fees stemming from medical care required to treat complications. The parental permission form has been modified to provide further information for participating families. The form has

also been modified to provide a space for each parent's signature, in accordance with 45 CFR 46.408(b). [Appendix VI – Modified Parental Permission Form].

Review by other groups

The study has also been reviewed by the Data Safety Monitoring Board for the Cystic Fibrosis Foundation (see memo dated 07/01/02). They found that the bronchoscopies and the bronchoalveolar-lavage do represent a minor increase over minimal risk but they do not believe that the study presents unacceptable risk overall. In their letter to Dr. Noah, they indicate that "the risk of moderate to severe complication is very low in otherwise stable children; especially when done with the help of an anesthesiologist. Death is virtually unheard of in this setting in children." They also note that "although BAL such as this is not the standard of care currently, it is growing in use as guidance of therapy. Many centers are using BAL on a regular basis so this study is only moderately outside the standard of care at UNC." The DSMB further found the potential for benefit for all subgroups of children in this study.

This group, with considerable expertise in the area under study, concluded that the proposed study was implicitly approvable under 45 CFR 46.405 or 46.407. While this came after and did not alter the determinations of our local IRB, it is reflective of the subjective nature of this process, and of the blurry boundary at which the risk-benefit ratio for this particular study lies. In any case, the DSMB likewise encouraged Dr. Noah to pursue approval and conduct this study.

Description of study in grant

This study was originally included in the grant application that we have provided to you. The proposed study modifies the population from children undergoing surgery for complications related to meconium ileus to the children described herein. Despite this modification, the principal investigator for the grant, Dr. Richard Boucher, has agreed that this project will be funded through the SCOR grant to UNC, as a substitute for the meconium ileus study. Thus, the proposed study remains under NIH funding.

We appreciate your assistance and look forward to your further review. Please don't hesitate to contact us if further questions arise.

Sincerely,

Stephen A. Bernard, M.D
Chair, Committee on the Protection of the Rights of Human Subjects (IRB)

Daniel K. Nelson, MS, CIP
Director, Office of Human Research Studies

Enclosures:

Appendix IA:	Missing Items: Award Application
IB:	Missing Items: Minutes of meetings of December 17, 2001, February 4, 2002 and April 15, 2002
Appendix II:	References
Appendix III:	Conscious Sedation Protocol, Bronchoscope Cleaning Protocol
Appendix IV:	Complication Data at UNC
Appendix V:	Modified Parental Permission Form

cc: Terry Noah, M.D.